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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,382	KUPPER ET AL.	
	Examiner	Art Unit	
	Michael D. Burkhart	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,10,12-16,21-23,25-30 and 33-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10,12-16,21-23,25-30 and 33-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 February 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/6/02, 7/8/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-32 were pending. By preliminary amendment filed 2/19/2002, claims 8, 11, 17-20, 24, 31, and 32 were cancelled and claims 33-40 were added. As a result, claims 1-7, 9-10, 12-16, 21-23, 25-30, and 33-40 are pending.

Priority

This application, filed 7/8/2002, is a 371 of PCT EP 00/07768, filed 8/10/2000. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

Claim 21 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

Claim 16 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 13 recites a helper construct, claim 16 recites a helper cell containing the construct.

Information Disclosure Statement

The information disclosure statement filed 7/8/2002 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each reference listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered. Reference 2, Kern et al., is in the German language, and no explanation of its relevance has been provided. See MPEP 609.

Drawings

The drawings are objected to because they are partially labeled in German and therefore incapable of interpretation. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the

applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9-10, 12-16, 22-23, 25-30, and 33-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim a recombinant RNA molecule comprising a noninfectious Coxsackie virus group B (CVB) genome and at least one foreign gene; virions containing said genome; vectors encoding said RNA, its complementary DNA, or any necessary helper sequences; and therapeutic compositions comprising said RNA or virions. Applicants disclose the Coxsackievirus serotype B3 genome, a map and plasmid from said genome, and PCR primers and methods to prepare constructs from said genome. The claims read on a genus of recombinant RNA molecules, foreign genes, virions, helper constructs, and therapeutic compositions, all based on any CVB.

The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed

correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention. In the instant case, applicants only disclose the limited number of noninfectious Coxsackievirus B3 genomes (with capsid and protease 2A deleted) and helper vectors found in figures 4 and 5, respectively. Neither applicants nor the prior art disclose other noninfectious CVB genomes, helper vectors, nor which foreign genes may be suitable. Applicants claim the noninfectious CVB genomes, associated helper vectors, and foreign genes by function only, without a correlation between structure and function. Given the diversity of CVBs and foreign genes claimed, it is unpredictable that the noninfectious Coxsackievirus B3 and helper vectors described could be used to make a noninfectious genome from any CVB and foreign gene. The diversity of the CVBs and foreign genes, lack of disclosure regarding other noninfectious CVB genomes, sequences, and helper vectors, would require the skilled artisan to conclude that the examples presented by the applicants are not sufficient to describe the claimed genus.

Claims 1-7, 9-10, 12-16, 22-23, 25-30, and 33-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics,* Inc. 8

USPQD2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is a conclusion reached by weighing several factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQQ2d 1400 (Fed. Cir. 1988) and include the following:

Unpredictability of the art. The only disclosed use for the claimed vectors is gene transfer, i.e. gene therapy. The art concerning expressing foreign DNA sequences in humans (gene therapy), is unpredictable. Dang et al. (Clin. Cancer Res., Vol. 5, p. 471-474, 1999) outline several factors limiting human gene therapy such as suboptimal vectors, lack of long term and stable gene expression, and host immune response to the vector. They further cite the findings of the Orkin-Motulsky Committee, commissioned by the director of the NIH, that found human gene therapy an immature science with limited understanding of gene regulation and disease models. Basak et al. (Viral Immun. Vol. 17, p. 182-196, 2004) teach that these problems have not been overcome. Furthermore, Basak et al. teach anti-viral immunity is a significant therapeutic obstacle (bottom of p. 183) because many individuals have pre-existing high titers of neutralizing antibodies and those who do not may be prone to acute toxic responses at high viral doses. By proposing to use a pathogenic human virus (Coxsackievirus B3) for gene therapy, even in a noninfectious form, applicants encounter the same enablement problems listed above. However, applicants do not disclose a single working example of foreign gene expression as claimed, let alone how to overcome the art-recognized problems found in the current expression systems outlined above. It is completely unpredictable that a noninfectious Coxsackievirus B3 genome containing a foreign gene could be used as an expression system in a host cell. The production of Coxsackievirus

viral RNA involves a transient double-stranded RNA intermediate in the cytoplasm, a powerful inducer of the PKR and interferon response in eukaryotic cells (Gauntt et al., Front. in Biosci., Vol. 8, p. 23-35, 2003, see in particular page 27, second column, section 3.10). These antiviral molecules stimulate the innate immune response and lead to apoptosis and inflammation, ultimately destroying the host cell.

State of the art. The state of the art regarding the expression of foreign genes for human gene therapy, particularly with a noninfectious CVB genome, is poorly developed. The development of such genomes, associated helper vectors, helper cells, and methods would have to be done empirically, along with the identification of the appropriate foreign genes.

Number of working examples. Applicants have provided no working examples of: a noninfectious CVB genome expressing a foreign gene in a host; associated helper vectors; virions bearing said CVB genome; or pharmaceutical compositions comprising said genome.

Amount of guidance. Applicants provide vector diagrams and PCR primers for a noninfectious Coxsackievirus B3 genome, lacking the capsid and protease 2A sequences, and associated helper vectors. These are prophetic examples only, there is no demonstration that the claimed noninfectious genome has been produced, let alone that it can be used to express foreign genes. Applicants provide no direction or vector diagrams for production of other noninfectious CVB genomes, helper vectors, foreign genes, how to produce the claimed virions, or how to practice the claimed gene therapy. The specification requires the skilled artisan to practice trial and error experimentation with

different noninfectious CVB genomes, foreign DNA sequences, helper vectors and helper cells to determine which (if any) will be compatible as claimed.

Scope of the invention. The claims are broad in nature and read on any noninfectious CVB genome and foreign gene expressed in any host.

Nature of the invention. The invention involves the unpredictable art of foreign genes in a host and producing noninfectious CVB genomes.

Level of skill in the art. While the level of skill in the art is high, the unpredictability of the art, lack of guidance, broad scope of the claims and poorly developed state of the art would require that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9-10, 12, 22-23, 25-30, and 33-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, the phrase "for example" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). This rejection affects all dependent claims.

Regarding claims 1, 10, 28, 29, 34, 39, and 40 the phrase "preferably" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). This rejection affects all dependent claims.

Claims 9 and 34 recite the term "derived from." This term is indefinite because it is not clear how close to the original Coxsackievirus the recombinant virion might be. This rejection affects all dependent claims.

Claims 13 and 36 recite the limitation "coding sequences" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 23, 26, 27, and 30 are vague because it cannot be determined if the claimed kit or therapeutic compositions are separate from the DNA molecules (claims 23, 26) or virions (claims 27 and 30). It would be remedial to amend the claims to recite kits comprising DNA or virions.

Conclusion

No claims are allowed.

The closest prior art is exemplified by Tracy et al. (WO 98/39426, cited by applicants), which teaches the use of attenuated (as opposed to noninfectious as the instant claims) Coxsackievirus B3 to express murine Il-4.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael D. Burkhart
Examiner
Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER